REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully traversed. Pursuant to 37 CFR § 1.21, attached as an Appendix is a Version With Markings to Show Changes Made.

The rejection of claim 23 under 35 U.S.C. § 112 (1st para.) for failure to satisfy the written description requirement is respectfully traversed in view of the above amendments.

The rejection of claims 19 and 21-23 under 35 U.S.C. §102(b) as anticipated by Armstrong, et. al., "Pre-Oligodendrocytes from Adult Human CNS," J. Neurosci. 12(4): 1538-47 (1992) ("Armstrong") is respectfully traversed.

Armstrong discloses culturing white matter from human patients undergoing partial temporal lobe resection for intratable epilepsy to determine whether oligodendrocyte precursor cells are present in the adult human central nervous system. These cultures contained cells that expressed antigens recognized by the O4 monoclonal antibody. Selective inhibition of these O4-positive cells resulted in inhibition of *in vitro* development of oligodendrocytes. It is theorized that O4-positive cells appear to develop into oligodendrocytes, so they are referred to as pre-oligodendrocytes. However, these pre-oligodendrocytes do not divide in response to growth factors that trigger mitosis of neonatal oligodendrocyte progenitors. Since the pre-oligodendrocytes of Armstrong and the oligodendrocytes they produce do not undergo mitosis when treated with mitosis-triggering agents, it is clear that these cells are not mitotic. By contrast, the oligondendrocyte progenitors in accordance with the present invention are clearly mitotic as indicated by the following passage on page 22 of the present application:

> These data indicate that the adult human subcortex harbors a population of residual, mitotically-competent oligodendrocyte progenitor cells. The cells constitute a discrete population of bipolar blasts, distinct from mature oligodendrocytes. The progenitors were mitotically competent, and as such, distinct from the much larger population of mature, apparently post-mitotic oligodendrocytes. These cells were antigenically immature ($A2B5^+/O4^-$) when isolated, but matured ($O4^+/O1^+$) over several weeks in culture. Cell-specific targeted reporting, achieved by transfecting the overall white matter pool with plasmids of GFP placed under the control of the early promoter for oligodendrocytic CNP, allowed the live-cell identification of these progenitor cells. This, in turn, provided a means for their isolation and purification, by fluorescence-activated cell sorting based on P/hCNP2-driven GFP expression.

In the outstanding office action, the U.S. Patent and Trademark Office ("PTO") asserts that Armstrong inherently produces the claimed enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, because Armstrong and applicants used a similar procedure to obtain cells from a similar source. Applicants disagree.

First, Armstrong attempts the use of monoclonal antibody O4-defined separation of the oligodendrocyte progenitor cells, a method previously shown effective in isolating oligodendrocyte progenitor cells from rats (Second Declaration Of Steven A. Goldman Under 37 C.F.R. §1.132 ("Second Goldman Declaration") ¶ 5). Applicants used the CNP/2 promoter-based separation specifically to address Armstrong's failure to isolate the oligodendrocyte progenitor cells (Id.). Applicants' work subsequently demonstrated that human O4-defined cells are post-mitotic and do not act as mitotic oligodendrocyte progenitor cells in any event (Id.).

Second, the tissue extraction techniques used by Armstrong were substantially and critically different from applicants (Second Goldman Declaration ¶ 6). In particular, on page 539, Armstrong describes a glial isolation procedure in which white matter was subjected to an enzymatic dissociation procedure involving 2 sequential enzymatic treatments (Id.). Enzymatic treatment solution 1 contained trypsin, papain, collagenase, and DNase, while subsequent enzymatic treatment solution 2 contained trypsin, collagenase, and DNase (Id.). By contrast, the procedure used by applicants, as described on page 16, lines 14-16 of the present application, involved treatment with papain and DNase (Id.). The reason that applicants did not use trypsin in this procedure is, because they discovered that trypsin, when used to enzymatically digest white matter, was so destructive that it caused the loss of both oligodendrocytes and oligodendrocyte progenitor cells (Id.). As a result, applicants modified their procedure to specifically omit trypsin and, only at that point, did they achieve viable extraction of oligodendrocyte progenitor cells (Id.). In view of applicants' exclusion of trypsin, it is clear that the claimed enriched or purified preparation of human mitotic oligodendrocyte progenitor cells were obtained by methods never reported by Armstrong (Id.). As a result, there is no basis to assume that Armstrong and applicants produce the same material.

Since Armstrong cannot be used as a proper basis to reject the claims, the rejection under 35 U.S.C. § 102 as anticipated by Armstrong should be withdrawn.

The rejection of claims 19 and 21-23 under 35 U.S.C. § 102(b) over Kirschenbaum, et. al., "*In Vitro* Neuronal Production and Differentiation by Precuror Cells Derived from the Adult Human Forebrain," Cerebral Cortex 6: 576-89 (1994) ("Kirschenbaum") is respectfully traversed.

The study described in Kirschenbaum was carried out in the laboratory of applicant Steven A. Goldman, M.D., Ph.D. who was the supervising scientist on the study and, therefore, this work is fully understood by Dr. Goldman (See Declaration of Steven A. Goldman under 37 C.F.R. § 1.132 which was filed on June 10, 2002 ("First Goldman Declaration") ¶ 5). Kirschenbaum cultures samples of adult temporal lobes under conditions suitable for neuronal differentiation, while exposed to ^{3}H-thymidine (Id.). These samples were incubated for 7-28 days, stained for neuronal and glial antigens, and autoradiographed (Id.). Neuron-like cells were found in explant outgrowths and monolayer dissociates of the subependymal zone and periventricular white matter but not the cortex (Id.). A small number of Map-2^{+} and Map-5^{+}/glial fibrillary acidic protein^{-} cells did incorporate ^{3}H-thymidine, suggesting neuronal production from precursor mitosis (Id.). However, the O4^{+} oligondendrocytes were postmitotic (Id.). Even though the abstract of Kirschenbaum states that "O4^{+} oligodendrocytes, although the predominant cell type, were *largely* postmitotic (emphasis added)", Dr. Goldman only said this, because he is reluctant to make conclusions in absolute terms (Id.). Nevertheless, it is clear from the following statement on page 582 of Kirschenbaum that, in fact, *all* of the oligodendrocytes were post-mitotic:

> These O4^{+}/GFAP$^{\pm}$ cells were mitotically quiescent; among a sample of 8044 such cells, culled from four plates of subcortical white matter (2011 ± 858.6 O4^{+} cells/plate, mean ± SD), *none* incorporated ^{3}H-thymidine *in vitro*, despite the frequent observation of ^{3}H-thymidine-labeled astrocytes in the same plates (emphasis in original).

(Id.). The failure of the Kirschenbaum study to identify mitotic oligodendrocyte progenitor cells caused Dr. Goldman to continue working to identify and produce such cells which efforts were ultimately successful in producing the invention of the present application (Id.).

In the outstanding office action, the PTO refers to the discussion on page 582 of Kirschenbaum where the following statements are made:

> [A] second comparatively uncommon category of O4^{+} cells was characterized by a larger (15-25 mm), flatter, and more substrate-apposed soma; each cell projected several relatively thick, long and tapering, unbranched processes. These cells are constituted <1% of the O4^{+} population, and frequently

> incorporated ^{3}H-thymidine. The onotogeny and fate of these O4^{+}/^{3}H-thymidine^{+} cells are now being evaluated separately . . . .

This second category of O4^{+} cells do not include human mitotic oligodendrocyte progenitor cells as claimed (Second Goldman Declaration ¶ 8). The claimed human mitotic oligodendrocyte progenitor cells are initially O4^{-}, are small bodies with diameters of less than 10 μm (about 6-7 μm), and have an ovoid morphology (Id.). The size and shape of such cells are demonstrated in Figures 2 A-C and 3 A-H of the present application (as well as on page 7, line 19 to page 8, line 3 of the specification) and in Figures 2 A-C and 3 A-H of Roy, et. al., "Identification, Isolation, and Promoter-Defined Separation of Mitotic Oligodendrocyte Progenitor Cells From the Adult Human Subcortical White Matter," J. Neurosci. 19(22): 9986-95 (1999) ("Roy") (Id.). Roy has a disclosure corresponding to that of the present application and includes and defines size bars (Id.). The initial O4^{-} phenotype of the claimed human mitotic oligodendrocyte progenitor cells is set forth on page 22, lines 11-12 of the present application (Id.). By contrast, the passage of Kirschenbaum immediately quoted above teaches that the second comparatively uncommon category of cell is O4^{+}, has a size of 15-25 μm, is flat, and projects long and tapering processes (Id.). In view of these distinctions, it is apparent that Kirschenbaum's second category of cells do not constitute human mitotic oligodendrocyte progenitor cells, as claimed (Id.).

Since Kirschenbaum does not disclose mitotic oligodendrocyte progenitor cells as claimed, the rejection based on this reference should be withdrawn.

The rejection of claims 19 and 21-22 under 35 U.S.C. § 103 for obviousness over U.S. Patent No. 5,276,145 to Bottenstein ("Bottenstein") is respectfully traversed.

Bottenstein is directed to substantially purified preparations containing a neural progenitor regulatory factor that is important in regulating and coordinating production of oligodendrocytes and type 2 astrocytes (First Goldman Declaration ¶ 6). The identification and purification of this factor was carried out with brain cells derived from neonatal rats of 1-3 days of age. These cells represented a mixture of cell types that included "progenitors", "Type 2 Astrocytes", "Early Oligodendrocytes", "Late Oligodendrocytes", "Total Oligodendrocytes", "Type 1 Astrocytes", and "Microglia" (Id.).

There are fundamental differences between the biology of rat and human oligodendrocyte progenitor cells (First Goldman Declaration ¶ 7). These are unaddressed in Bottenstein, which discusses findings limited to neonatal rat brain (Id.). Whereas rat oligodendrocytes appear to retain mitotic potential, human oligodendrocytes do not (see Kirschenbaum) (Id.). As a result, the oligodendrocyte progenitor cell of the rat brain cannot be

considered homologous to its human counterpart (Id.). In particular, methods that permit the selective extraction and/or growth of oligodendrocyte progenitors from the rat brain do not differentiate between oligodendrocyte progenitor cells and mature oligodendrocytes able to re-enter the mitotic cycle (Id.). In humans, these constitute two discrete phenotypes, lineally related but temporally distinct (Id.). The present invention teaches the selective acquisition of a highly enriched – to virtual purity - mitotically-competent oligodendrocyte progenitor cell pool, operationally separate and distinct from post-mitotic or mature oligodendrocytes (Id.).

Bottenstein was directed at the enrichment of glial progenitor cells from newborn rat brain (First Goldman Declaration ¶ 8). Newborns have an abundant population of still-developing oligodendrocyte progenitor cells that may constitute a significant fraction of all of the cells in neonatal brain tissue (Id.). Bottenstein reported that >30% of the cells of its tissue dissociates expressed the marker of this phenotype (Id.). With the addition of B104 conditioned media and the neural progenitor regulatory factor, this fraction increased to just over 40% (Id.). The nature of these cells is that of a still-mixed pool, in that the following populations appear to be represented by Bottenstein's data: astrocytes, oligodendrocytes, and a mixture of oligodendrodendroglial lineage cells of widely different developmental stages (Id.).

In contrast to the cells acquired from newborn rats using the Bottenstein protocol, the present invention is achieved with a procedure that permits, in both young and old humans, the selective extraction of progenitor cells strongly biased to oligodendrocytic phenotype, and allows the purification of these cells, including those from tissues in which they are scarce (e.g., postnatal and adult brain tissues harboring <1% of the desired oligodendrocyte progenitor cell type) (First Goldman Declaration ¶9.). In Example 5 of the present patent application, the virtual purification of oligodendrocyte progenitor cells from tissues with a P/CNP2 promoter-targeted FACS-defined incidence of <1% was reported (Id.). This constituted a far greater enrichment of the oligodendrocyte progenitor cell (i.e. 170-fold) than that achieved by Bottenstein (i.e. less than 1.5-fold) and yields a far more pure product of oligodendrocyte progenitor cells (Id.).

In contrast to Bottenstein, the human oligodendrocyte progenitor cell populations achieved through the protocols of the present invention are virtually pure as to phenotype (First Goldman Declaration ¶ 10). Compare Figure 5B to its control, Figure 5A (Id.). In Figure 5A, the gated single cell represents the false-positive sort incidence (Id.). Such incidences constitute <1% of the frequency of events noted in Figure 5B, indicating >99% purity of the P/CNP2:hGFP-sorted oligodendrocyte progenitor cells (Id.). This can be modulated as a function of sort speed to achieve any desired degree of purity, the trade-off being lower yields as higher degrees of purification are achieved (Id.). By virtue of the high-purity extraction attainable by fluorescence-activated cell

sorting, the progenitor cells produced according to the present invention are never exposed to paracrine factors released by other cells, after removal from tissue (Id.). This permits their maintenance in an undifferentiated and phenotypically-unbiased state, in contrast to the mixed cellular milieu afforded by Bottenstein, in which non-oligodendrocytic and non-glial progenitor-derived phenotypes remain abundant (Id.).

As a result of these considerations, the selective propagation of mitotically-active oligodendrocyte progenitor cells from the neonatal rat brain, as taught by Bottenstein, does not predict the successful isolation of mitotic oligodendrocyte progenitor cells from postnatal or adult human brain tissue (First Goldman Declaration ¶ 11).

In the outstanding office action, the PTO states that Bottenstein is not distinguishable from the claimed invention, because a mixture of cell types can still constitute the claimed enriched or purified preparation. However, if Bottenstein's propagation of cells from rat brain would not have made obvious (let alone feasible) the preparation of the claimed human mitotic oligodendrocyte progenitor cells, then it is of no moment that the claims encompass a mixture of cell types. Further, by the above amendments, dependent claims of the present application are distinguishable from Bottenstein on their own. In particular, claim 29 requires that an oligodendrocyte specific promoter function in all cells of the enriched or purified preparation, while claims 27 and 28 mandate that the preparation of human mitotic oligodendrocyte progenitors be at least 90% pure and 99% pure, respectively. Support for the limitations of claim 29 is found on page 10, line 29 to page 11, line 3 of the present application. As to the limitations of claims 27-28, Figures 5 A-B of the present application teach that purity can be elevated from<1% to >99% by the present invention (See First Goldman Declaration ¶ 10). From this teaching, it is apparent that any purity between these values can be achieved with the present invention, including a purity of 90%, as set forth in claim 27.

For all of these reasons, the obviousness rejection of claims 19 and 21-22 over Bottenstein should be withdrawn.

The rejection of claims 19 and 21-23 under 35 U.S.C. § 103 for obviousness over U.S. Patent No. 6,245,564 to Goldman, et. al. ("Goldman '564") is respectfully traversed.

The only basis for regarding Goldman '564 as prior art is under 35 U.S.C. § 102(e). However, as demonstrated by the assignment records of Goldman '564 (Exhibit 1 attached hereto) and the present application (Exhibit 2 attached hereto), all right, title, and interest in Goldman '564 and the present application is held by Cornell Research Foundation,

Inc. ("CRF"). Further, at the time the subject inventions of Goldman '564 and the present application were made, they were assigned or subject to an obligation of assignment to CRF (Exhibit 3, Statement of Attorney of Record Under M.P.E.P. § 706.02(l)(1) Concerning Common Ownership, attached hereto).

Under 35 U.S.C. § 103(c), which applies to utility applications filed on or after November 29, 1999, "[s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." Although 35 U.S.C. § 103(c) does not apply to the parent of the present application, which was filed on March 31, 1999, the Manual of Patent Examining Procedure states that "[t]he mere filing of a continuing application on or after November 29, 1999, with the required evidence of common ownership, will serve to exclude commonly owned 35 U.S.C. § 102(e) prior art that was applied, or could have been applied, in a rejection under 35 U.S.C. § 103 in the parent application." M.P.E.P. § 706.02(l)(1), at 700-36 (8th edition, Aug. 2001). Thus, since the present application was filed after November 29, 1999, and was accompanied by the required evidence of common ownership of Goldman '564 and the present application by CRF, the obviousness rejection based on Goldman '564 is not proper and must be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: November 1, 2002

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Date: 11/1/02 | Wendy L. Barry

APPENDIX
Version With Markings to Show Changes Made
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In reference to the amendments, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In the Claims:

Please amend claims 25-26 as follows:

25. (Amended) The [method] enriched or purified preparation of human mitotic oligodendrocyte progenitor cells according to claim [24] 29, wherein the mitotic oligodendrocyte progenitor cells are from a post-natal human.

26. (Amended) The [method] enriched or purified preparation of human mitotic oligodendrocyte progenitor cells according to claim [24] 29, wherein the mitotic oligodendrocyte progenitor cells are from an adult human.